Prenatally Diagnosed Uncommon Mosaic Autosomal Trisomy

Bom-Yi Lee[1], So-Yeon Park[1], Moon-Hee Lee[1], Jin-Woo Kim1, Ju-Yeon Park[1]
Eun-Young Choi[1], Yeon-Woo Lee[1], Ah-Rum Oh1, Shin-Young Lee[1],
Min-Hyung Kim[2] and Hyun-Mee Ryu[1, 2]

Laboratory of Medical Genetics[1], Cheil General Hospital and Women's Healthcare Center,
Kwandong University College of Medicine, Seoul, Korea
Department of Obstetrics and Gynecology[2], Cheil General Hospital and Women's Healthcare Center,
Kwandong University College of Medicine, Seoul, Korea

Prenatal diagnosis of rare autosome mosaicism involvingchromosomes other than chromosome 13, 18, 21 or the sex chromosome is encountered prognostic dilemma during genetic counseling. We report four cases of level III uncommon mosaicism of trisomy 5, 16 and 20,diagnosed prenatally. In case 1 with mosaic trisomy 20, there was a higher mosaic ratio of trisomy 20 in the repeat amniocentesis (62.1%) than in the first (36.6%) with normal fetal ultrasound finding except for a relatively small aorta on a 3-vessel view of the fetal heart. Case 2 showed a low rate of mosaic trisomy 20 (5.25%) in cultured amniocytes but normal karyotype in the repeat amniocentesis, who delivered a normal healthy baby. Case 3 showed a 13.6% of trisomy 16 mosaicism in the 30 cells of cultured amniocytes. Sixty cells from a fetal blood sample at termination showed non-mosaic 46,XX normal karyotype, while skin fibroblasts had 22.5% trisomy 16 in 40 metaphases. The autopsy showed ventricular septal defect (VSD). Case 4 with low grade mosaicism (10.5%) of trisomy 5 resulted in elective termination, though the ultrasoumd showed growsly normal fetus. Although level III mosaicism is regarded as true mosaicism, it is difficult to predict the outcome of the fetus with rare mosaic autosome trisomy. Therefore mosaic autosome trisomy of fetus should be carefully interpreted with more various approaches including repeat sampling and targeted fetal ultrasound.

Key Words: Autosomal mosaicism, Trisomy 5, Trisomy 16, Trisomy 20

Introduction

Autosome trisomies have been detected in almost all autosomes except for trisomy 1 in spontaneous abortion series and they account for 60% of all abnormalities. Also, autosome true mosaicism except for marker chromosomes accounts for 44-47% of all mosaicism in analyzed amniocytes[1)]. The most common mosaic autosome trisomies are detected in chromosomes 13, 18, and 21, while other autosome mosaic trisomies are relatively rare. Mosaicism found in prenatal diagnosis is considered very carefully due to the various degree of mosaicism and specimen type, depending on the time of pregnancy. Clinical anomalies of rare mosaic autosome trisomies have not been characterized clearly because of a lack of reported cases. The most common clinical abnormalities in mosaic trisomies are reported intrau-

접 수: 2009년 6월 4일
수정본접수: 2009년 6월 18일
게재승인일: 2009년 6월 22일
게 재 일: 2009년 6월 30일
책 임 저 자: 류현미
우100-380 서울시 중구 묵정동 1-19
제일병원 의학연구소 유전학연구실
Tel: 02)2000-7678, Fax: 02) 2278-4574
E-mail: hmryu@yahoo.com

terine growth restriction (IUGR), mental retardation, and heart, renal,and/or facial anomalies[2]. It may be useful to pursue confirmatory chromosomal studies through several specimens and to study maternal serum screening test and high-resolution ultrasound examinations in thesecond trimester and molecular analysis to rule out uniparental disomy (UPD). Here, we report four cases of prenatal mosaic trisomy 5, 16 and 20 that may be helpful in understanding prenatal mosaic autosome trisomy and diagnosing future cases.

Case report

1. Case 1; 47,XY,+20/46,XY

A 40-year-old woman underwent amniocentesis for advanced maternal age at 15 weeks of gestation. The fetal karyotype revealed 47,XY,+20[15]/46,XY[26]. The repeat amniocentesis at 17 gestational weeks showed 47,XY,+20[55]/46,XY[27]. Ultrasound at 21 weeks of gestation showed grossly normal fetus except for a relatively small aorta on a 3-vessel view of the fetal heart. Elective termination of the pregnancy was chosen. However, an autopsy was not performed, per parental request.

2. Case 2; 47,XX,+20/46,XX

A 32-year-old mother was referred for amniocentesis at 16 weeks gestation because of evidence of increased risk (1:218) for Down syndrome in maternal serum screening test. The chromosomal study showed 47,XX,+20[3]/46,XX[54] in independent cultured lines, but the repeat amniocentesis at 18 weeks revealed 46,XX, normal in 110 metaphases. The female baby weighing 3,700 grams was delivered at term and is currently healthy at 17 months of age.

3. Case 3; 47,XX,+16/46,XX

A 34-year-old woman was referred for amniocentesis at 19 weeks gestation for elevated risk of NTD and Down syndrome in maternal serum screening test. The initial amniocentesis showed 47,XX,+16[3]/46,XX[27] and a repeat amniocentesis revealed 47,XX,+16[6]/46,XX[38]. A targeted sonography at 22 weeks of gestation showed VSD with coarctation of the aorta. The parents decided to terminate the pregnancy. In the post-termination analysis, umbilical cord blood karyotype showed 46,XX[60] normal, while the skin fibroblast karyotype was 47,XX,+16[9]/46,XX[31]. On autopsy, VSD and a small left ventricle were found.

4. Case 4; 47,XY,+5/46,XY

A amniocentesis was performed due to increased risk of neural tube defect (NTD) and Edward syndrome in maternal serum screening test of the 29-year-old mother. The result was 47,XY,+5[8]/46,XY[68]. The parents refused a repeat amniocentesis for confirmation. Fetal sonography findings at 18 weeks were normal. Abortion was induced at 21 weeks. An autopsy was not available with a birth weight of 240 grams.

Discussion

Mosaic autosome trisomies found in prenatal diagnosis show various ratios of mosaicism according to the specimen and depending on the time of pregnancy. They should be given careful consideration when diagnosing mosaicism prenatally. There are confined mosaicism only observed in extraembryonic tissues and pseudomosaicism considered as in vitro cultural artifact aside from a constitutional mosaicism of embryo[3].

Of the four cases presented here, case 1 had Level III mosaicism (36.6%) of trisomy 20 on the amniocentesis, while the repeat amniocetesis revealed ahigher mosaicism ratio (62.1%) for an extra chromosome 20. Case 2 was referred for an increased risk for Down syndrome and had a low rate (5.3%) of level III mosicism of trisomy 20in three-line cultured amniocytes. However, repeat amniocentesis revealed a non-mosaic 46,XX normal karyotype in 110 metaphase cells. This

Table 1. Summary of the Present 4 Cases of Autosomal Trisomy

Case	Age/ Parity	Indication for fetal karyotpe	US	Karyotype	Delivery	Postnatal study/ Follow Up
1	40/G4 P1 SA1	AMA	Relatively small aorta	*1st amniocentesis (17.6 wks)* 47,XY,+20[15]/46,XY[26] Level III *2nd amniocentesis (21 wks)* 47,XY,+20[55]/46,XY[27] Level III	TOP at 21 wks	Not available
2	32/G2 A2	Down SD(+) on maternal serum screening	Grossly normal	*1st amniocentesis (18 wks)* 47,XX,+20[3]/46,XX[54] Level III *2nd amniocentesis (19 wks)* 46,XX[110]	Delivered at term	Healthy by 17 months
3	29/G1	NTD & Down SD (+) on maternal serum screening	VSD	*1st amniocentesis (19 wks)* 47,XX,+16[3]/46,XX[27] Level III *2nd amniocentesis (22 wks)* 47,XX,+16[6]/46,XX[38] Level III	TOP at 24 wks	*Skin fibroblast* 47,XX,+16[9]/46,XX[31] Level III *Lymphocytes* 46,XX,[60] *Autopy;* VSD
4	34/G1	NTD & Edward SD (+) on maternal serum screening	Grossly normal	*1st amniocentesis (18.1 wks)* 47,XY,+5[8]/46,XY[68] Level III *2nd amniocentesis* Refused	TOP at 21 wks	Not available

Abbreviations : US, fetal ultrasound findings; G, gravida; P, para; A, abortion; SA, spontaneous abortion; AMA, advanced maternal age; wks, gestational weeks; TOP, termination of pregnancy; SD, syndrome; NTD, neural tube defect; VSD, ventricular septal defect

suggests that case 2 might be confined placental mosaicism while case 1 might be constitutional mosaicism. The most common mosaic trisomy 20 on the amniocentesis is detected in 16% of the prenatal mosaicism[4], and 5−10% of these cases show abnormal outcomes at delivery[5, 6]. Although the clinical symptoms have not been clearly classified yet, over 90% of reported abortuses and newborns with mosaic trisomy 20 diagnosed prenatally show grossly normal phenotypes[5, 7]. An abnormal mosaic trisomy 20 cell line is rarely found postnatally in lymphocytes or other tissue cultures. It is thought that mosaic trisomy cell lines would be lost in the process of trisomy rescue during fetal development or that mosaic trisomy 20 cell lines are confined to extraembryonic regions. The major clinical anomalies occurring in mosaic trisomy 20 cases are IUGR, heart, renal and/or facial anomalies, language delays and William syndrome[8]. Additionally, it is not clear that the degree of trisomy 20 mosaicism is related to the severity of clinical anomalies[9].

The initial cytogenetic analysis in case 3 showed Level III mosaicism (10%) for an extra chromosome 16 with a slightly raised ratio of 13.6% on the second analysis. Fetal sonography findings showed VSD with coarctation of the aorta. In the post−termination analysis, we found 22.5% mosaic trisomy 16 in 40 cells of the skin fibroblasts but not in the 60 metaphase lymphocytes. Autopsy examination showed VSD and a small left ventricle. Non−mosaic trisomy 16 detected prenatally accounts for about 6% of miscarriages[10]. The major clinical anomalies reported include VSD, artrial septal defect, and skeletal, gastrointestinal, and renal anomalies[2]. Mosaic trisomy 16 diagnosed prenatally is also rarely confirmed in blood or other tissues postnatally. Therefore, the proportion of abnormal cell lines would decline over time. Our case also showed VSD on a fetal

sonography which a colony with trisomy 16 was not found in post-terminated blood lymphocytes as in previous reports[11]. Additionally, the fetus in this case was a female, which is concordant with a report by Benn[12] that suggests that mosaic trisomy 16 occurs more often in females.

Case 4 was a case of level III mosaic trisomy 5 with a 10.5% ratio in three-line cultured amniocytes referred for elevated risk for NTD and Edward syndrome at 16 weeks gestation. However, ultrasound showed grossly normal fetus. To date, nine cases of mosaic trisomy 5 have been reviewed and six cases showed grossly normal phenotypes[13]. The other three cases had facial dysmorphism, congenital heart disease (CHD) and IUGR, and trisomy 5 cell lines were detected in the cord blood, skin, testis and placenta. There has been a report of a case of high level (80%) trisomy 5 mosaicim that led to a normal live birth at six months. Somatic tissues and placental tissues had normal karyotypes[14]. It is thought that the extra chromosome 5 was lost through the fetal trisomic rescue process. However, there have been no reports on UPD (5) so far.

In prenatal diagnosis of rare mosaic autosome trisomy, we should consider clinical information with indications of laboratorial analysis and fetal ultrasound findings. Second,the results should be compared to patterns found in previous cases relating to the type of specimen and the stage of pregnancy at which it was obtained. All available referred specimens should be analyzed cytogenetically, including chorionic villus sampling, amniocytes, other fibroblasts, and cord blood, to confirm the significance of mosaicism in order to make a final decision. Third, it also should be ruled out UPD resulted in the normal cell line during the consequence of trisomic rescue that make complicate to the accurate diagnosis. Finally, in cases with very low ratios of mosaic cell lines, the potential trisomy effects on distinct tissues over a lifetime should be considered[15].

We present four cases of uncommon mosaic autosomal trisomy diagnosed prenatally. Although level III mosaicism is regarded as true mosaicism, it is difficult to predict the outcome of fetus with rare mosaic autosome trisomy. Therefore, more various approaches should be provided in prenatal diagnosis, and mosaic autosome trisomy of fetus should be carefully interpreted. We expect them our cases to be helpful in the diagnosis and genetic counseling of other mosaic autosomal trisomy cases.

국문초록

산전에서 성염색체와 13번, 18번, 21번 염색체를 제외한상염색체의 모자이시즘은 발생빈도가 낮고 증례보고가 적어서 예후 예측이 어렵다. 저자들은 삼염색체성 5번, 16번, 20번의 산전진단 4례를 보고하고자 한다. 모자익 삼염색체성 20번 2례 중 증례 1은 양수 염색체 검사에서 36.6%의 모자이시즘을 보였으나 재검한 양수 검사에서는 보다 높은 빈도 (62.1%)를 보였다. 증례 2에서는 양수 염색체 검사에서 모자이시즘 삼염색체성 20번이 5.25% 였으나, 재검 양수천자결과는 정상 핵형을 보였다. 증례 3은 30개의 양수세포에서 삼염색체성 16번의 모자이시즘이 13.6% 관찰되었다. 임신 종결 후, 총 60개의 태아 혈액 세포에서 모자이시즘 없는 정상 핵형이 관찰되었으나 태아의 피부 섬유아세포에서 얻은 40개의 중기상 세포에서는 22.5%의 삼염색체성 16번 모자이시즘을 보였다. 부검결과 심실중격결손(ventricular septal defect)이 관찰되었다. 증례 4는 76개의 중기상 세포에서 10.5%의 삼염색체성 5번 모자이시즘을 보였으나 태아의 초음파검사에서는 정상소견을 보였다. Level III 모자이시즘은 진성 모자이시즘으로 간주되지만 발생빈도가 낮은 상염색체의 삼염색체성 모자이시즘은 태아의 예후를 예견하기 어려우므로 산전 진단시 여러 조직의 재검 및 태아 초음파 소견과 함께 다양한 임상적 접근 방법으로 그 해석에 신중을 기해야 할 것으로 사료된다.

References

1) Hsu LYF, Yu MT Richkind KE, Van Dyke DL, Crandall BF, Saxe DF, et al. Incidence and significance of chromosome mosaicism involving an autosomal structural abnormality diagnosed prenatally through amniocentesis: a collaborative study. Prenat Diagn 1996; 16:1-28.

2) Hsu LYF, Yu MT, Neu RL, Van Dyke DL, Benn PA, Bradshaw CL, et al. Rare trisomy mosaicism diagnosed in amniocytes, involving an autosome other than chromosomes 13, 18, 20 and 21:karyotype/phenotype correlations. Prenat Diagn 1997;17:3:201-42.
3) Gardner RJM and Sutherland GR, Second edition, Chromosome abnormalities and genetic counseling, Oxford monographs on medical on genetics no. 29. 1996.
4) Kuwahara RT, Henson T, Tunca Y, Wilroy SW. Hyperpigmentation along the lines of Blaschko with associated chromosome 14 mosaicism. Pediatr Dermatol 2001;18:360-1.
5) Hsu LYF, Kaffe S, Perlis TE. Trisomy 20 mosaicism in prenatal diagnosis - a reviewand update. Prenat Diagn 1987;7:581-96.
6) Hsu LYF, Kaffe S, Perlis TE. A revisit of trisomy 20 mosaicism in prenatal diagnosis - an overview of 103 cases. Prenat Diagn 1991;11:7-15.
7) Wallerstein R, Yu MT, Neu RL, Benn P, Lee Bowen C, Crandall B,et al. Common trisomy mosaicism diagnosed in amniocytes involvingchromosome 13, 18, 20 and 21: karyotype-phenotype correlations. Prenat Diagn 2000;20:103-22.
8) Hartmann A, Hofmann UB, Hoehan H, Broecker EV, Hamm H. Postnatal confirmation of Prenatally diagnosed Trisomy 20 mosaicism in a patient with linear and whorled nevoid hypermelanosis. Prediatr Dermatol 2004;21:636-41.
9) Wallerstein R, Twersky S, Layman P, Kernaghan L, Aviv H, Pedro HF, et al. Long term follow-up of developmental delay in a child with prenatally-diagnosed trisomy 20 mosaicism. Am J Med Genet 2005;137A: 94-7.
10) Warbuton D, De novo balanced chromosomerearrangements and extra marker chromosomes identified at prenatal diagnosis: clinical significance and distribution of breakpoints. Am J Med Genet 199149:995-1013.
11) Velissariou V, Antoniadi T, Gyftodimou J, Bakou K, Grigoriadou M, Christopoulou S, et al. Maternal uniparental isodisomy 20 in a foetus with trisomy 20 mosaicism: Cloinical, cytogenetic and molecular analysis. Eur J Hum Genet 2002;10:694-8.
12) Benn P. Trisomy 16 and trisomy 16 mosaicism: a review. Am J Med Genet 1998;79:121-33.
13) Villa N, Redaelli S, Borroni C, Colombo C, Roncaglia N, Salsa E. Fetal trisomy 5 mosaicim: Case report and literature review. Am J Med Genet Part A 2007;143A: 2343-6.
14) Richkind KE, Apostol RA, Puck SM. Prenatal detection of trisomy 5 mosaicism with normal outcome, Prenat Daign 1987;7:143.
15) Robinson WP, McGillivray B, Lewis MES, Arbour L, Barrett I, Kalousek DK. Prenatally detected trisomy 20 mosaicism. Prenat Diagn 2005;25:239-44.